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Hippocampal subfields predict positive symptoms in schizophrenia: First evidence from brain morphometry

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Alterations of hippocampal anatomy have been reported consistently in schizophrenia. Within the present study, we used FreeSurfer to determine hippocampal subfield volumes in 21 schizophrenic patients. A negative correlation between PANSS-positive symptom score and bilateral hippocampal subfield CA2/3 as well as CA1 volume was found on high-resolution magnetic resonance images. Our observation opens the gate for advanced investigation of the commonly reported hippocampal abnormalities in schizophrenia in terms of specific subfields.
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Introduction

Alterations of hippocampal anatomy have consistently been reported in schizophrenia.[1] It has been hypothesized that resulting memory problems lead to increases of illusory pattern completion and are therewith involved in the generation of psychotic symptoms due to dysfunctional association forming.[2] In particular, the so-called autoassociative learning mechanism within the subfield cornu ammonis (CA) 3 together with CA1 allows for rapid binding of events that co-occur. Postmortem studies have reported reduced size and altered dendritic arborization of CA3 pyramidal neurons, predominantly in patients with positive symptoms.[3] However, the role of hippocampal CA subfields volume for positive symptoms has not been investigated *in vivo*.

Methods

We studied 21 schizophrenic patients (mean age = 34, 2 ± 8.2 years; five female; number of episodes = 2.5 ± 2.0; age of onset = 26.4 ± 7.8 years; 19 medicated with atypicals) giving written informed consent with the Positive and Negative Syndrome Scale (PANSS).[4] Hippocampal subfields volume was assessed fully automatic with FreeSurfer[5] on the average of 2–4 (mean = 3.4 ± 0.9) T1-weighted magnetic resonance images (3 T Siemens Trio; MPRAGE, resolution $1 \times 1 \times 1\,mm^3$). The computational model by van Leemput[5] incorporates a prior distribution that makes predictions about where neuroanatomical labels are expected to occur. This prior is based on a generalization of various probabilistic atlases, and is automatically learned from manual segmentations of the hippocampal formation in MRI images. A likelihood distribution then predicts how the labeled image, on which each voxel is assigned a unique neuroanatomical label, translates into an individual's MRI image. We focussed on the volume of the entire hippocampus, CA1, CA2/3, CA4/dentate gyrus, subiculum and presubiculum, disregarding fimbria and hippocampal fissure, because the later two are the smallest subfields that are considerably less reliably segmented[5]and disregarding the so-called 'hippocampus' subsegment that contains mainly the tail of the hippocampus where subfields were not discernable.

Results

We observed a negative Pearson's correlation between PANSS-positive symptom score (M = 12. 43, s.d. = 4.27) and bilateral hippocampal subfield CA2/3 volume ($r(21) = -0.46$, $P < 0.05$) as well as CA1 volume ($r(21) = -0.44$, $P < 0.05$, Figures 1 and 2, Table 1), indicating that patients with stronger positive symptoms have smaller CA2/3 and CA1 subfields. No other subfield showed significant correlations neither with the Positive Syndrome score ($P > 0.26$) nor with the Negative Syndrome score (M = 16.05, s.d. = 4.74, $P > 0.42$). Although the results do not survive conservative Bonferroni correction for multiple testing, the fact that not only bilateral CA2/3 and CA1 but also right and left structures separately survive statistical thresholding with $P < 0.05$ is remarkable. The subfield volumes do not correlate with chlorpromazine equivalents of neuroleptic medication (CA2/3: $r(21) = 0.04$, $P = 0.86$; CA1: $r(21) = 0.00$, $P = 0.99$).

Discussion

The results are compatible with models of hippocampal CA3 processes interacting with CA1 in the generation of positive symptoms.[2] These hippocampal subfields have been suggested to act as a binding module for cortical circuits containing weakly related sensory representations. CA3 in particular has been proposed to create representations of space and time as a basis of conscious awareness.[6]

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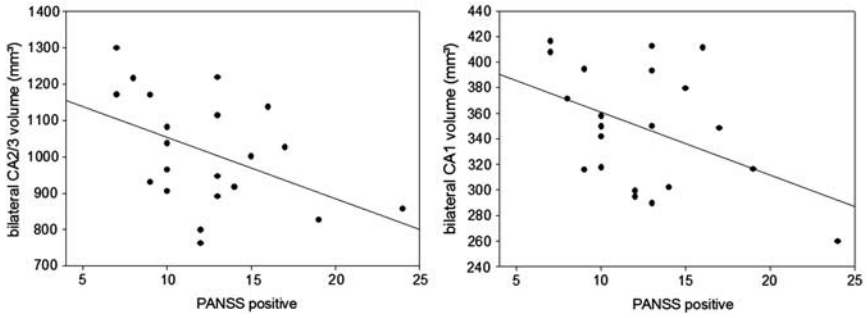

Figure 1 Negative correlation between the positive symptom subscale of the Positive and Negative Syndrome Scale (PANSS) and bilateral hippocampal CA2/3 and CA1 subfield volume.

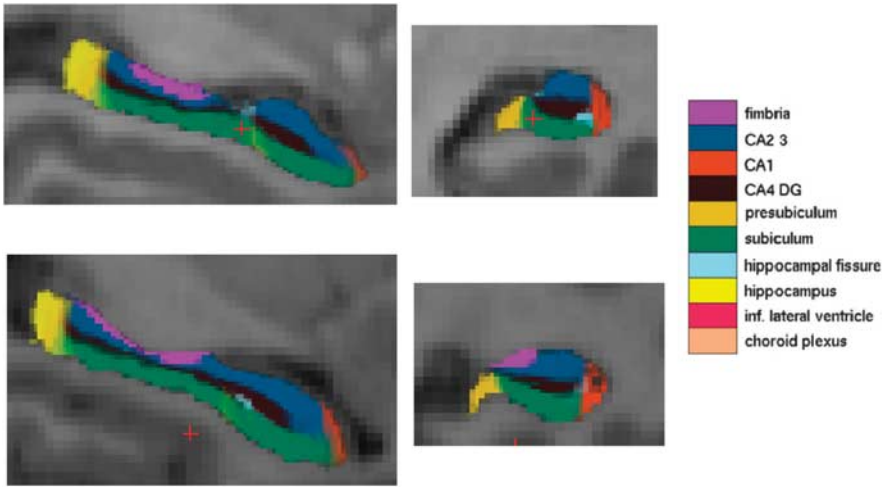

Figure 2 Left hippocampal subfield segmentation of two exemplary subject.

Table 1 Mean ± s.d. of bilateral larger hippocampal subfield volumes (in mm³) and its correlation with Positive and Negative Syndrome Score

Hippocampal subfields	*Mean (s.d., in mm³)*	*Correlation with positive symptoms (Pearson's correlation coefficient)*	*Correlation with negative symptoms (Pearson's correlation coefficient)*
Whole hippocampus	7010 (817)	−0.26	−0.07
CA1	350 (46)	**−0.44***	0.03
CA2/3	1013 (149)	**−0.46***	−0.07
CA4, dentate gyrus	563 (78)	−0.20	−0.08
Subiculum	669 (73)	−0.13	−0.19
Presubiculum	453 (40)	−0.19	−0.11

*Indicates correlations with $P<0.05$.

A subfield dysfunction would integrate sensory representations abnormally resulting in positive symptomatology; for instance, hallucinations.[2] Furthermore, it has been suggested that the disinhibition of hippocampal regions can stimulate hyperdopaminergic states and therewith produce psychosis.[7]

Our observation opens the gate for advanced investigation of the commonly reported hippocampal abnormalities in schizophrenia in terms of specific subfields. However, replication of results is needed in a larger sample of unmedicated patients with further differentiation of CA2/3 volumes. Furthermore, a limitation of the present study is the relatively low, albeit common, resolution of $1 \times 1 \times 1\,mm^3$. Future studies should consider using a sequence with a higher spatial resolution.

Conflict of interest

The authors declare no conflict of interest.

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